# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-464**

**21-466**

# MICROBIOLOGY REVIEW

## MICROBIOLOGY REVIEW
### DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

**NDA #:** 21-464, 21-466, 21-266 and 21-267

**REVIEWER** : Kalavati Suvarna
**CORRESPONDENCE DATE** : 05-13-03, 09-03-03, 09-17-03
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**REVIEW ASSIGN DATE** : 05-15-03, 09-04-03, 09-22-03
**REVIEW COMPLETE DATE** : 09-29-03

**SPONSOR:** C. P. Pharmaceuticals International C.V.
c/o Pfizer Inc.
235 East 42nd Street,
New York, NY 10017.

**SUBMISSION REVIEWED:** N-000 (AZ); N-000 (C, C)

**DRUG CATEGORY:** Anti-fungal

**INDICATION:** Treatment of esophageal candidiasis

**DOSAGE FORM:** Oral tablets and Intravenous injection

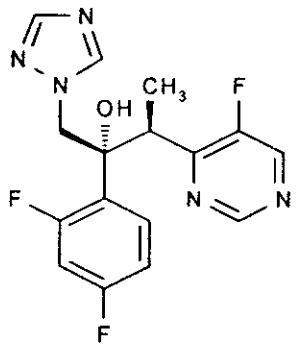
**PRODUCT NAMES:**

a. **PROPRIETARY:** Vfend®

b. **NONPROPRIETARY:** Voriconazole, UK-109,496

c. **CHEMICAL:** (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol

**STRUCTURAL FORMULA:**




Molecular weight: 349.3
Empirical formula: $C_{16}H_{14}F_3N_5O$

**SUPPORTING DOCUMENTS:** NDA# 21-266, NDA# 21-267

**TABLE OF CONTENT**

## 1. EXECUTIVE SUMMARY:

The sponsor is seeking approval of voriconazole for the treatment of esophageal candidiasis. Voriconazole is approved for the treatment of invasive aspergillosis and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species in patients intolerant to other therapy. The proposed dose for the treatment of esophageal candidiasis is same as that for the treatment of invasive aspergillosis.

The *in vitro* activity of voriconazole was examined against 5540 clinical isolates of *Candida* species by the NCCLS method (M27A) for the *in vitro* susceptibility testing of yeasts. The voriconazole MIC values against the different *Candida* species ranged from 0.006 to >16 µg/ml. However, the breakpoints for voriconazole have not been established.

Voriconazole was active in normal and/or immunocompromised guinea pigs infected with *C. albicans* (including an isolate with reduced susceptibility to fluconazole), *C. krusei* or *C. glabrata*. The endpoint in these studies was reduction in mycological burden in tissues.

In the clinical trials (reviewed in the original submission NDA #21-266/21-267), the majority of isolates collected at baseline from the patients with esophageal candidiasis were *Candida albicans*. The number of patients with esophageal candidiasis due to *Candida* species other than *C. albicans* was small. To evaluate the activity of voriconazole against *Candida* species other than *C. albicans*, the data from clinical studies evaluating efficacy of voriconazole in the treatment of esophageal and non-esophageal candidiasis were pooled. The clinical data from the pooled patient population suggests that voriconazole has activity against *C. glabrata* (69%; 18/26), *C. krusei* (82%; 9/11), *C. tropicalis* (63%; 5/8) and *C. parapsilosis* (80%; 4/5). However, the number of patients with infections due to *C. tropicalis* and *C. parapsilosis* was small. Based on the overall activity *in vitro* and *in vivo*, *C. glabrata* and *C. krusei* may be included in the microbiology section of the label. However, the label should specify that the majority of patients with esophageal candidiasis had infection due to *C. albicans*.

## 2. INTRODUCTION AND BACKGROUND:

The subject of this NDA supplement is Vfend® (voriconazole), an approved drug for the treatment of invasive aspergillosis and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species (in patients intolerant or refractory to other therapy). In this re-submission, the sponsor is seeking approval for the treatment of esophageal candidiasis. The patients will be administered 200 mg oral tablets every 12 hours for patients weighing ≥ 40 kg and 100 mg every 12 hours for patients weighing ≤ 40 kg. The proposed dose for the treatment of esophageal candidiasis is same as the dose approved for the treatment of patients with invasive aspergillosis.

## 3. PRECLINICAL MICROBIOLOGY:

### 3.1. Mechanism of Action:

No new information was included in this submission. Voriconazole belongs to the azole class of antifungal agents and inhibit the enzyme, cytochrome P-450 dependent 14 α-lanosterol demethylase, essential for the synthesis of the fungal cell wall component, ergosterol (for details see microbiology review dated 11-02-01, NDA# 21-266/21-267, N-000).

### 3.2. Activity *in vitro* against *Candida* species:

No new information was included in this submission. The *in vitro* susceptibility testing of voriconazole against *Candida* species was performed using the National Committee for Clinical Laboratory Standards (NCCLS) method (M27A) for the *in vitro* susceptibility testing of yeasts. Please note that the breakpoints for voriconazole have not been established. The studies reviewed earlier (for details see microbiology review dated 11-02-01, NDA# 21-266/21-267, N-000) show variability in the *in vitro* activity of voriconazole against the different *Candida* species (voriconazole MIC values ranging from 0.006 to >16.0 μg/ml; Table 1). Additionally, no correlation was observed between the MICs values and clinical outcome.

Table 1: Summary of the *in vitro* activity of voriconazole against various *Candida* species conducted in different laboratories from studies submitted to original NDA.

| ***Candida* species** | **Number of isolates ($MIC_{90}$ in µg/ml)*** | | | | | **All isolates** | |
|---|---|---|---|---|---|---|---|
| | **Manavathu *et al.*, 1998** | **Ruhnke *et al.*, 1997** | **Literature 08/96-09/99** | **Clinical study 150-608** | **Clinical study 150-305** | **N** | **Range of $MIC_{90}$** |
| *C. albicans* | 1 (0.015)** | 105 (0.78) | 2349 (0.015->8) | 176 (0.015) | 545 (0.39) | 3176 | 0.015->8 |
| *C. glabrata* | 1 (0.5)** | ND | 791 (0.25 - 8.0) | 42 (1.0) | 56 (1.56) | 890 | 0.25 - 8.0 |
| *C. tropicalis* | 1 (0.25)** | ND | 428 (0.06 - >16) | 50 (8.0) | 5 (0.012 - 0.049) | 484 | 0.06 - >16 |
| *C. krusei* | ND | ND | 173 (0.06 - 2.0) | ND | 17 (0.19-0.39) | 190 | 0.06 - 2.0 |
| *C. parapsilosis* | 1 (0.125)** | ND | 553 (0.007 - 1) | 38 (0.015) | 5 (0.006 - 6.3) | 597 | 0.006 – 6.3 |
| *C. lusitaniae* | 1 (0.5)** | ND | 13 ( 0.5) | ND | ND | 14 | 0.5 |
| *C. guilliermondii* | 1 (0.25)** | ND | 51 (4.0) | ND | ND | 52 | 0.25 - 4.0 |
| *C. dubliniensis* | ND | ND | 100 (0.03) | ND | ND | 100 | 0.03 |
| *C. hisitaniae* | ND | ND | 17 (0.06) | ND | ND | 17 | 0.06 |
| *C. kefyr (C. pseudotropicalis)* | 1 (0.125)** | ND | 4 (0.06 - 0.125) | ND | ND | 5 | 0.06 – 0.125 |
| *C. stellatoidea* | 1(0.125)** | ND | 1 (0.125)** | ND | ND | 2 | 0.125 |
| *C. lipolytica* | ND | ND | 1 (0.125)** | ND | ND | 1 | 0.125 |
| *C. pelliculosa* | ND | ND | ND | 2 (0.25) | ND | 2 | 0.25 |

ND= Not done; N = total number of isolates.

* the $MIC_{90}$ values were determined if the number of isolates ≥ 10

** represents range of MICs for isolates where $MIC_{90}$ values were not determined or the MICs of the isolate if only one was tested.

### 3.3. Activity *in vivo* against *Candida* species:

No new information was included in this submission. The studies reviewed earlier (for details see microbiology review dated 11-02-01, NDA# 21-266/21-267, N-000) demonstrated the activity of voriconazole against *Candida* species in normal and immunocompromised (neutropenic) guinea pigs. In all these studies, voriconazole was administered orally at 1 hour post-infection and the mycological burden was measured 16 or 24 hours after discontinuation of therapy.

Voriconazole (5 mg/kg b.i.d for 5 days) was shown to be effective in reducing the fungal burden (4 $log_{10}$) in the kidneys of immunocompetent and immunocompromised guinea pigs infected with *C. albicans* strain Y01.02 (MICs for fluconazole, voriconazole, itraconazole and amphotericin B were 0.78, 0.024, 0.098, and 0.098 µg/ml, respectively), 16 hours after discontinuation of therapy. However, a two fold higher dose of voriconazole (10 mg/kg b.i.d for 5 days) was required for similar reduction in fungal burden (3 $log_{10}$) in the kidneys of immunocompromised guinea pigs infected with *C. albicans* strain Y01.358 with reduced susceptibility to fluconazole (MICs for fluconazole, voriconazole, itraconazole and amphotericin B were 100, 0.78, 0.19, and 0.19µg/ml, respectively).

In immunocompromised guinea pigs infected with *C. krusei* or *C. glabrata*, voriconazole (10 mg/kg b.i.d for 5 days) reduced the fungal burden in the kidneys by 2 $log_{10}$ when measured 16 hours after discontinuation of therapy.

In another study, voriconazole (≥ 5 mg/kg b.i.d for 7 days) administered one hour post-infection reduced the fungal burden in the brain, liver and kidneys of neutropenic guinea pigs infected with *C. krusei* when measured 24 hours after discontinuation of therapy.

Overall, oral voriconazole was effective in reducing the fungal burden in the tissues of normal and/or immunocompromised guinea pigs infected with *C. albicans*, *C. glabrata* and *C. krusei*.

**3.4. Clinical Microbiology:**

One pivotal (#150-350) and two supportive (#150-309 and #150-604) clinical studies were included to support the indication of esophageal candidiasis. Upon request, the sponsor provided additional data for 17 patients with infections due to *Candida* species other than *C. albicans*. This information became available after submission of the original NDA.

**Study 150-305:** This was a randomized, double-blind, double dummy, multi-center, active control study conducted to evaluate the efficacy of voriconazole (200 mg bid for 14 days) in the treatment of esophageal candidiasis. Fluconazole (200mg qd for 14 days) was used as a comparator (for details on the study design please refer to the Medical Officer's review dated 05-24-02). The patients were considered evaluable if they had esophageal candidiasis confirmed by endoscopy and culture, received treatment for at least 12 days, had an end of therapy (EOT) endoscopic evaluation, showed evidence of treatment compliance, and had not received any other antifungal medication. The primary efficacy parameter was endoscopic findings. The endoscopic result at EOT was compared to the result at baseline and assessed as cured (normal endoscopy at EOT), improved (abnormal endoscopy at EOT but at least a 1 grade improvement over baseline), or failed (no change or deterioration compared to baseline). The mycological response was defined as eradicated (no lesions present or no growth of *Candida* on culture and no microscopic evidence of *Candida* in brushing or biopsy sample if lesions were present) or persisted (lesions present with a positive culture for *Candida* and/or microscopic evidence of *Candida* in brushing or biopsy samples).

Of the 391 patients enrolled, 200 were randomized to the voriconazole arm and 191 to the fluconazole arm. Of the 200 patients in the voriconazole arm, 81 were excluded from the efficacy analysis. In the fluconazole arm, 47 out of the 191 patients were excluded. The reasons for exclusion of the above patients were as follows: (a) only one endoscopic exam performed, (b) received <12 days of study drug, (c) received other systemic antifungals <3 days prior to study entry, and (d) no mycological evidence of esophageal candidiasis. The results in Table 2 show that a majority of the evaluable patients (voriconazole, n = 119; fluconazole, n = 144) had baseline infection due to *C. albicans* alone (voriconazole, n = 110; fluconazole n = 137). Of the remaining 9 patients in the voriconazole arm, 6 had baseline infection due to *C. glabrata* (4 patients had mixed infections due to *C. albicans* plus *C. glabrata*) and 3 due to unidentified *Candida* species. Of the remaining 7 patients in the fluconazole arm, 3 had baseline infection due to *C. glabrata* (1 patient had mixed infections due to *C. albicans* plus *C. glabrata*), 2 had mixed infection due to *C. krusei* plus *C. albicans*, and 2 had infections due to unidentified *Candida* species.

Since the primary endpoint for the study was endoscopic results, mycological evaluations by culture, microscopy or histology was not performed in a majority of the patients. The clinical and mycological responses of esophageal candidiasis patients treated with voriconazole or fluconazole are shown in Tables 2 and 3. In the voriconazole arm, 108/110 (98%) patients with esophageal candidiasis due to *C. albicans* had a successful clinical outcome at EOT. All patients with single infections due to *C. glabrata* (2/2), unidentified *Candida* species (3/3) or mixed infections due to *C. glabrata* plus *C. albicans* (4/4) had a successful clinical outcome. Mycological eradication at EOT was observed in 74/81 (91%) patients with esophageal infection due to *C. albicans*, 1/2 (50%) due to *C. glabrata*, 2/3 (67%) due to *C. glabrata* plus *C. albicans* and 3/3 (100%) due to unidentified

*Candida* species. New infections due to *C. glabrata, C. krusei* or *C. famata* were observed in 5 patients during therapy.

At 4 weeks post-therapy, one of the evaluable patients in the voriconazole arm with baseline *C. albicans* infection relapsed. In addition, relapse was observed in 3 non-evaluable patients (1 with baseline *C. albicans* and 2 with baseline *Candida* species).

In the fluconazole arm, a successful clinical outcome was observed in 130/137 (95%) patients with baseline infection due to *C. albicans*, 2/2 (100%) due to *C. glabrata*, 1/1 due to *C. glabrata* plus *C. albicans*, 2/2 (100%) due to *C. krusei* plus *C. albicans* and 2/2 (100%) due to *Candida* species at EOT. Mycological eradication at EOT was observed in 82/100 (82%) patients with infection due to *C. albicans*, 1/2 (50%) due to *C. glabrata*, 1/1 due to *Candida* species. New infections developed in 10 patients due to *C. glabrata, C. krusei, C. parapsilosis* or *C. famata* during therapy.

Relapse was observed in 9 evaluable patients (8 had baseline *C. albicans* and 1 with *C. krusei* plus *C. albicans*) and 2 non-evaluable patients with baseline *C. albicans* infection, at 4 weeks post-therapy,.

Overall, voriconazole was effective in the treatment of esophageal candidiasis due to *C. albicans*. The number of patients with infection due to *Candida* species other than *C. albicans* was too small to draw any conclusions (Table 4).

**Studies 150-309 and 150-604:** In order to evaluate the activity of voriconazole against *Candida* species other than *C. albicans*, the clinical and mycological responses at EOT of patients with systemic or invasive *Candida* infections intolerant or refractory to an approved antifungal agent in the open label, non-comparative studies 309 and 604 were analyzed (for details on the study design, please see medical officer's review dated 08-31-01, NDA #21-266/21-267, N-000). The clinical response was defined as **complete** (resolution of all signs and symptoms and/or bronchoscopic abnormalities due to fungal infection), **partial** (major improvement in the signs and symptoms and/or bronchoscopic abnormalities due to fungal infection), **stable** (minor or no improvement in signs and symptoms of disease) or **failure** (deterioration in signs and symptoms of disease). Mycological response was defined as **eradication** (absence of baseline fungal pathogen by culture and microscopy or histology), **presumed eradication** (inferred in patients with complete clinical and radiological response), **persistence** (presence of baseline fungal pathogen by culture, microscopy or histology), or **indeterminate** (data was inadequate for classification of a response). These studies included patients with esophageal and non-esophageal candidiasis. The responses for the two groups are shown below separately. The data on the clinical and mycological responses of 17 new patients from studies 309 and 604 that became available since the last submission were included in the analysis.

There were 7 patients (4 new patients identified by the letter N following the patient identification number) with **esophageal candidiasis** due to *C. krusei, C. glabrata* or *C. parapsilosis* (Table 5). One patient with baseline infection due to *C. krusei* alone did not eradicate the yeast but showed a complete clinical response. Of the remaining 6 patients, *C. albicans* was isolated in addition to *C. krusei, C. glabrata* or *C. parapsilosis* at baseline in 5 patients and *C. albicans* plus *C. inconspicua* was isolated in addition to *C. krusei* in 1 patient. All the 6 patients with mixed infection showed a favorable clinical response. The yeasts were eradicated or presumed eradicated in 1 patient with *C. krusei* + *C. albicans* + *C. inconspicua* infection, 3 with *C. glabrata* + *C. albicans* and 1 with *C. parapsilosis* + *C. albicans* infection. The data was not available for 1 patient with mixed infection due to *C. krusei* + *C. albicans*. None of the patients relapsed at 4 weeks post-therapy.

Table 2: Mycological and clinical responses of all patients in study 150-305 by baseline pathogen at EOT and follow-up (4 weeks).

| Baseline pathogen (N) | Population (N) | Mycological response | Clinical response* | | |
|---|---|---|---|---|---|
| **Voriconazole (200)** | | | | | |
| *C. albicans* (176) | Evaluable (110) | 74 Eradicated | 74 Success $^{R1}$ | | |
| | | 7 Persisted | 6 Success $^{2Cg; 1Cf}$ | 1Failed | |
| | | 29 Not done | 28 Success | 1Failed | |
| | Non evaluable (66) | 16 Eradicated | 15 Success | 1 Failed | |
| | | 10 Persisted | 7 Success $^{1Cg; 1Ck; R1}$ | 3 Failed | |
| | | 40 Not done | 4 Success | | 36 Not done |
| *C. glabrata* (4) | Evaluable (2) | 1 Eradicated[a] | 1 Success | | |
| | | 1 Persisted[a] | 1 Success | | |
| | Non evaluable (2) | 1 Eradicated[a] | 1 Success | | |
| | | 1 Not done | | | 1 Not done |
| *C. glabrata* + *C. albicans* (5) | Evaluable (4) | 2 Eradicated | 2 Success | | |
| | | 1 Persisted | 1 Success | | |
| | | 1 Not done | 1 Success | | |
| | Non evaluable (1) | 1 Persisted | 1 Success | | |
| *C. krusei* + *C. albicans* (2) | Non evaluable (2) | 1 Eradicated | 1 Success | | |
| | | 1 Not done | | | 1 Not done |
| *Candida* species (13) | Evaluable (3) | 3 Eradicated | 3 Success | | |
| | Non evaluable (10) | 5 Eradicated | 5 Success $^{R2}$ | | |
| | | 5 Not done | 2 Success $^{1Cp}$ | | 3 Not done |
| **Fluconazole (191)** | | | | | |
| *C. albicans* (175) | Evaluable (137) | 82 Eradicated | 80 Success $^{1Cg, R7}$ | 2 Failed | |
| | | 18 Persisted | 14 Success $^{2Cg; 3Ck; 1Cf; 1Cp; R1}$ | 4 Failed $^{2Cg}$ | |
| | | 37 Not done | 36 Success | 1 Failed | |
| | Non evaluable (38) | 9 Eradicated | 9 Success $^{R2}$ | | |
| | | 6 Persisted | 5 Success | 1 Failed | |
| | | 23 Not done | 3 Success | 1 Failed | 19 Not done |
| *C. glabrata* (4) | Evaluable (2) | 1 Eradicated | 1 Success | | |
| | | 1 Persisted | 1 Success | | |
| | Not evaluable (2) | 2 Not done | | | 2 Not done |
| *C. glabrata* + *C. albicans* (2) | Evaluable (1) | 1 Persisted | 1 Success | | |
| | Non evaluable (1) | 1 Persisted | 1 Success $^{1Ck}$ | | |
| *C. krusei* + *C. albicans* (2) | Evaluable (2) | 2 Not done | 2 Success $^{R1}$ | | |
| *C. tropicalis* (1) | Non evaluable (1) | 1 Persisted | 1 Success | | |
| *C. parapsilosis* + *C. albicans* (1) | Non evaluable (1) | 1 Eradicated | 1 Success | | |
| *Candida* species (6) | Evaluable (2) | 1 Eradicated | 1 Success | | |
| | | 1 Not done | 1 Success | | |
| | Non evaluable (4) | 1 Eradicated | 1 Success | | |
| | | 3 Not done | 1 Success | | 2 Not done |

Evaluable = patients with *Candida* esophagitis (confirmed by endoscopy and culture) who had received at least 12 days of treatment, had end of therapy endoscopic assessment, showed evidence of treatment compliance, and had not receive any forbidden medication.

N = no of subjects; NA = not applicable; * = Success includes cured and improved response

$^{R}$ = patients with relapse, number following the R indicates the number of patients that relapsed.

$^{Cg}$ = New infection with *C. glabrata* and the number preceding Cg indicates the number of patients with the new infection

$^{Ck}$ = New infection with *C. krusei* and the number preceding Ck indicates the number of patients with the new infection

$^{Cp}$ = New infection with *C. parapsilosis* and the number preceding Cp indicates the number of patients with the new infection

[a] = previously classified as *C. albicans* in the "eff_myc" dataset for study but sponsor has stated that the species was identified as *C. glabrata* at the central laboratory after the original NDA was submitted.

Table 3: Summary of the clinical and mycological responses of evaluable patients with esophageal candidiasis at EOT in study 150-305.

| Pathogen | Endoscopic response* | Mycological eradication |
|---|---|---|
| **Voriconazole** | | |
| *C. albicans* | 108/110 (98%) | 74/81 (91%) |
| *C. glabrata* | 2/2 (100%) | 1/2 (50%) |
| *C. albicans* + *C. glabrata* | 4/4 (100%) | 2/3 (67%) |
| *Candida* species | 3/3 (100%) | 3/3 (100%) |
| **Fluconazole** | | |
| *C. albicans* | 130/137 (95%) | 82/100 (82%) |
| *C. glabrata* | 2/2 (100%) | 1/2 (50%) |
| *C. glabrata* + *C. albicans* | 1/1 | 0/1 |
| *C. krusei* + *C. albicans* | 2/2 (100%) | 0/0 |
| *Candida* species | 2/2 (100%) | 1/1 |

* includes cured and improved responses

Table 4: Summary of the clinical and mycological outcome by baseline pathogen in patients with esophageal candidiasis who had endoscopic and/or mycologic assessment at EOT (study 150-305).

| Pathogen# | Favorable endoscopic response* | Mycological eradication* |
|---|---|---|
| **Voriconazole** | | |
| *C. albicans* | 134/140 (96%) | 90/107 (84%) |
| *C. glabrata* | 8/8 (100%) | 4/7 (57%) |
| *C. krusei* | 1/1 | 1/1 |
| **Fluconazole** | | |
| *C. albicans* | 147/156 (94%) | 91/115 (79%) |
| *C. glabrata* | 4/4 (100%) | 1/4 (25%) |
| *C. krusei* | 2/2 (100%) | 0/0 |
| *C. tropicalis* | 1/1 | 0/1 |
| *C. parapsilosis* | 1/1 | 1/1 |

# Some patients had more than one species isolated at baseline
* patients with endoscopic and/or mycologic assessment at end of therapy

Table 5: Clinical and mycological response of patients with esophageal candidiasis due to *Candida* species other than *C. albicans* in studies 150-309/604.

| Patient ID* | Pathogen | Clinical Response | Mycological Response |
|---|---|---|---|
| *Voriconazole* | | | |
| 309 20051476N | *C. krusei* | Complete | Persistence |
| 309 02691162 | *C. krusei* + *C. albicans* | Complete | Indeterminate |
| 309 02691168N | *C. krusei* + *C.albicans* + *C. inconspicua* | Complete | Presumed eradication |
| 309 20051418 | *C. glabrata* + *C. albicans* | Partial | Presumed eradication |
| 309 02691169N | *C. glabrata* + *C. albicans* | Complete | Presumed eradication |
| 309 00141010 | *C. glabrata* + *C. albicans* | Complete | Eradication |
| 309 02691165N | *C. parapsilosis* + *C. albicans* | Complete | Presumed eradication |

* new patients were identified by the letter N following the patient identification number.

The data on the mycological and clinical responses of patients with esophageal candidiasis due to *Candida* species other than *C. albicans* from studies 305, 309 and 604 were pooled. The clinical and mycological responses of patients irrespective of mixed infections were determined (Table 6). Thus, a successful clinical outcome was observed in all 11 patients with *C. glabrata*. Of the 11 patients with *C. glabrata* infection, 10 had a mycological evaluation. The yeast was eradicated in 5 patients while in 2 patients, the yeast was presumed eradicated. Persistence of yeast was observed in 3 other

patients. All 4 patients with *C. krusei* infection showed a successful clinical outcome. The yeast were eradicated or presumed eradicated in 2 patients, while persistence was observed in 1 patient. No mycological evaluation was performed in the 4th patient. The patients (1 each) with infections due to *C. inconspicua* or *C. parapsilosis* also showed a successful clinical outcome and yeasts were presumed eradicated.

Table 6: Clinical and mycological outcome of patients with esophageal candidiasis due to *Candida* species other than *C. albicans* in studies 150-305, 150-309 and 150-604 by pathogen irrespective of mixed infection.

| Organism | Clinical success (%) | Mycological eradication |
|---|---|---|
| **Voriconazole** | | |
| *Candida glabrata* | 11/11 (100%) | 7/10 (70%)* |
| *Candida krusei* | 4/4 (100%) | 2/3 (67%)* |
| *Candida inconspicua* | 1/1 | 1/1* |
| *Candida parapsilosis* | 1/1 | 1/1* |
| **Fluconazole** | | |
| *C. glabrata* | 4/4 (100%) | 1/4 (25%) |
| *C. krusei* | 2/2 (100%) | 0/0 |
| *C. tropicalis* | 1/1 | 0/1 |
| *C. parapsilosis* | 1/1 | 1/1 |

* includes presumed eradication

The clinical and mycological responses of 34 patients (13 new patients identified by the letter N following the patient identification number) with **non-esophageal candidiasis** from studies 309 and 604 due to *Candida* species other than *C. albicans* are shown in Table 7. An overall (clinical + mycological) favorable response was observed in a small number of patients with non-esophageal candidiasis due to *Candida* species other than *C. albicans*. Irrespective of single or mixed infection (Table 8), the rate of successful clinical response in patients with non-esophageal candidiasis varied from 47 to 75% for *C. glabrata* (7/15), *C. krusei* (5/7), *C. tropicalis* (5/8), *C. parapsilosis* (3/4), *C. kefyr* (1/1) and *C. famata* (1/1). The rate of mycological eradication by baseline pathogen varied from 25 to 75% for *C. glabrata* (5/15), *C. krusei* (4/7), *C. tropicalis* (2/8), *C. parapsilosis* (3/4), *C. kefyr* (0/1) and *C. famata* (1/1). None of these patients relapsed at 4 weeks post-therapy.

The activity of voriconazole against *C. glabrata* from non-esophageal candidiasis patients appears to be lower than that against isolates from patients with esophageal candidiasis (Tables 6 and 8). However, the activity of voriconazole against *C. krusei* in the two candidiasis patient population appears to be similar (Tables 6 and 8). The pooling of clinical response data (Table 9) from patients with esophageal and non-esophageal candidiasis suggests that voriconazole has activity against *C. glabrata* (69%; 18/26) and *C. krusei* (82%; 9/11). This is supported by studies performed in immunocompromised guinea pigs infected with *C. krusei* or *C. glabrata*. The pooled data also suggests that voriconazole has activity against *C. tropicalis* (63%; 5/8) and *C. parapsilosis* (80%; 4/5). However, the number of patients with infections due to these 2 *Candida* species was small.

Table 7: Clinical and mycological responses of patients with non-esophageal candidiasis due to *Candida* species other than *C. albicans* in studies 150-309/604.

| Patient ID | Pathogen | Clinical Response | Mycological Response |
|---|---|---|---|
| *Voriconazole* | | | |
| 309 00611035N | *C. famata* | Complete | Presumed eradication |
| 309 20471780N | *C. glabrata* | Stable | Intermediate |
| 309 01201431 | *C. glabrata* | Stable | Persistence |
| 309 02201700N | *C. glabrata* | Failure | Persistence |
| 604 10716019 | *C. glabrata* | Complete | Presumed eradication |
| 604 10916242N | *C. glabrata* | Partial | Eradication |
| 604 60306256N | *C. glabrata* | Complete | Indeterminate |
| 604 10016163 | *C. glabrata* | Failure | Persistence |
| 604 10016164 | *C. glabrata* | Failure | Persistence |
| 604 10336151 | *C. glabrata* | Complete | Indeterminate |
| 604 10596063 | *C. glabrata* | Complete | Eradication |
| 309 02251483N | *C. krusei* | Failure | Indeterminate |
| 309 02631910N | *C. krusei* | Complete | Eradication |
| 604 10016075 | *C. krusei* | Stable | Intermediate |
| 604 10366024* | *C. krusei* | Complete | Eradication |
| 604 10496010 | *C. krusei* | Complete | Eradication |
| 309 20051477N | *C. parapsilosis* | Complete | Eradication |
| 604 10236124 | *C. parapsilosis* | Complete | Eradication |
| 604 10326022 | *C. parapsilosis* | Partial | Indeterminate |
| 309 01131028N | *C. tropicalis* | Failure | Indeterminate |
| 309 03001140** | *C. tropicalis* | Complete | Eradication |
| 604 10686119# | *C. tropicalis* | Partial | Indeterminate |
| 604 10366025 | *C. tropicalis* | Partial | Indeterminate |
| 604 10366192 | *C. tropicalis* | Stable | Eradication |
| 604 10496106 | *C. tropicalis* | Failure | Persistence |
| 604 10686119*** | *C. tropicalis* | Partial | Indeterminate |
| 604 10746103## | *C. albicans* | Partial | Indeterminate |
| 309 20471782N | *C. albicans* + *C. glabrata* | ND | ND |
| 604 10596276N | *C. albicans* + *C. glabrata* | Complete | Eradication |
| 604 10786079N | *C. albicans* + *C. glabrata* | Failure | Persistence |
| 604 10916126 | *C. albicans* + *C. glabrata* | Partial | Indeterminate |
| 309 01441180N | *C. glabrata* + *C. krusei* | Complete | Eradication |
| 309 01131011 | *C. kefyr* + *C. krusei* + *C. tropicalis* | Complete | Indeterminate |
| 604 10326050 | *C. parapsilosis* + *Fusarium* + *Trichosporon. beigetii* | Stable | Eradication |

* patient had new infection with *C. parapsilosis*
** patient had new infection with *C . lusitaniae*
***patient had new infection with *C. krusei*
# patient had new infection with *C. krusei* as per dataset. Note that the sponsor has stated the patient had *C. krusei* instead of *C. tropicalis* at baseline in the submission dated 09-03-03 but did not indicate the pathogen was reclassified. Hence, pathogen identified in the original NDA was used for analysis.
##Note that the sponsor has stated the patient had *C. krusei* instead of *C. albicans* at baseline in the submission dated 09-03-03 but did not indicate the pathogen was reclassified. Hence, pathogen identified in the original NDA was used for analysis.

Table 8: Clinical and mycological outcome by baseline pathogen irrespective of mixed infection in patients with non-esophageal candidiasis due to *Candida* species other than *C. albicans* in studies 150-309/604.

| Pathogen | Clinical success* | Mycological eradication** |
|---|---|---|
| **Voriconazole** | | |
| *Candida glabrata* | 7/15 (47%) | 5/15 (33%) |
| *Candida krusei* | 5/7 (71%) | 4/7 (57%) |
| *Candida tropicalis* | 5/8 (63%) | 2/8 (25%) |
| *Candida parapsilosis* | 3/4 (75%) | 3/4 (75%) |
| *Candida kefyr* | 1/1 | 0/1 |
| *Candida famata* | 1/1 | 1/1 |

* includes complete and partial responses
** includes presumed eradication.

Table 9: Summary of the clinical and mycological outcome of patients with candidiasis (esophageal + non-esophageal) due to *Candida* species other than *C. albicans* in studies 150-305, 150-309 and 150-604 by baseline pathogen irrespective of mixed infection.

| Pathogen | Clinical success* | Mycological eradication** |
|---|---|---|
| **Voriconazole** | | |
| *Candida glabrata* | 18/26 (69%) | 12/25 (48%) |
| *Candida krusei* | 9/11 (82%) | 6/10 (60%) |
| *Candida tropicalis* | 5/8 (63%) | 2/8 (25%) |
| *Candida parapsilosis* | 4/5 (80%) | 4/5 (80%) |
| *Candida kefyr* | 1/1 | 0/1 |
| *Candida famata* | 1/1 | 1/1 |
| *Candida inconspicua* | 1/1 | 1/1 |
| **Fluconazole** | | |
| *C. glabrata* | 4/4 (100%) | 1/4 (25%) |
| *C. krusei* | 2/2 (100%) | 0/0 |
| *C. tropicalis* | 1/1 | 0/1 |
| *C. parapsilosis* | 1/1 | 1/1 |

* includes complete, partial, cured and improved responses
** includes presumed eradication.

Overall, 4 patients with baseline infection due to *C. albicans* or an unidentified *Candida* species relapsed at 4 weeks post-therapy in the voriconazole arm compared to 11 patients in the fluconazole arm with baseline infection due to single infection with *C. albicans* or mixed infection with *C. albicans* plus *C. krusei* (Table 10). It is unclear if these relapses were due to development of resistance by *Candida* species to voriconazole.

Table 10: Summary of patients with esophageal candidiasis who relapsed at 4 weeks post therapy by baseline pathogen.

| Pathogen | Voriconazole (n) | Fluconazole (n) |
|---|---|---|
| *C. albicans* | 2 | 10 |
| *C. albicans* + *C. krusei* | 0 | 1 |
| *Candida* species | 2 | 0 |
| **Total** | **4** | **11** |

n = number of patients

## 4. CONCLUSIONS:

The sponsor is seeking approval of voriconazole for the treatment of esophageal candidiasis. The clinical study 150-305 demonstrated that voriconazole was as effective as fluconazole for the treatment of esophageal candidiasis due to *C. albicans*. The number of patients with esophageal candidiasis due to a *Candida* species other than *C. albicans* is too small to draw any conclusions. The

pooling of clinical response data (Table 9) from patients with esophageal and non-esophageal candidiasis suggests that voriconazole has activity against *C. glabrata* (69%; 18/26) and *C. krusei* (82%; 9/11). It appears that voriconazole has activity against *C. tropicalis* (63%; 5/8), and *C. parapsilosis* (80%; 4/5). However, the number of patients with infections due to these two pathogens is small.

The *in vitro* activity of voriconazole was tested against 890 isolates of *C. glabrata* and 190 isolates of *C. krusei* by the NCCLS method for susceptibility testing of yeasts (Table 1). The voriconazole MICs against the two *Candida* species ranged between 0.06 and 8 μg/ml.

In immunocompromised guinea pigs infected with *C. krusei* or *C. glabrata*, voriconazole (10 mg/kg b.i.d for 5 days) reduced the fungal burden in the kidneys by 2 $\log_{10}$ when measured 16 hours after discontinuation of therapy.

In another study, voriconazole (≥ 5 mg/kg b.i.d for 7 days) administered one hour post-infection reduced the fungal burden in the brain, liver and kidneys of neutropenic guinea pigs infected with *C. krusei* when measured 24 hours after discontinuation of therapy.

Based on the overall *in vitro*, animal and clinical data, *C. glabrata* and *C. krusei* may be included in the microbiology section of the label. However, the label should be specified that the majority of patients with esophageal candidiasis had infection due to *C. albicans*.

## 5. LABEL:

### 5.1. Sponsor's proposed label:

The sponsor's proposed changes to the current approved label are underlined.

**MICROBIOLOGY**

**Mechanism Of Action**
Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

**Activity *In Vitro* And *In Vivo***
Voriconazole has demonstrated *in vitro* activity against *Aspergillus fumigatus* isolates as well as *A. flavus, A. niger* and *A. terreus*. Variable *in vitro* activity against *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani*

(see INDICATIONS AND USAGE and CLINICAL STUDIES - Invasive Aspergillosis).

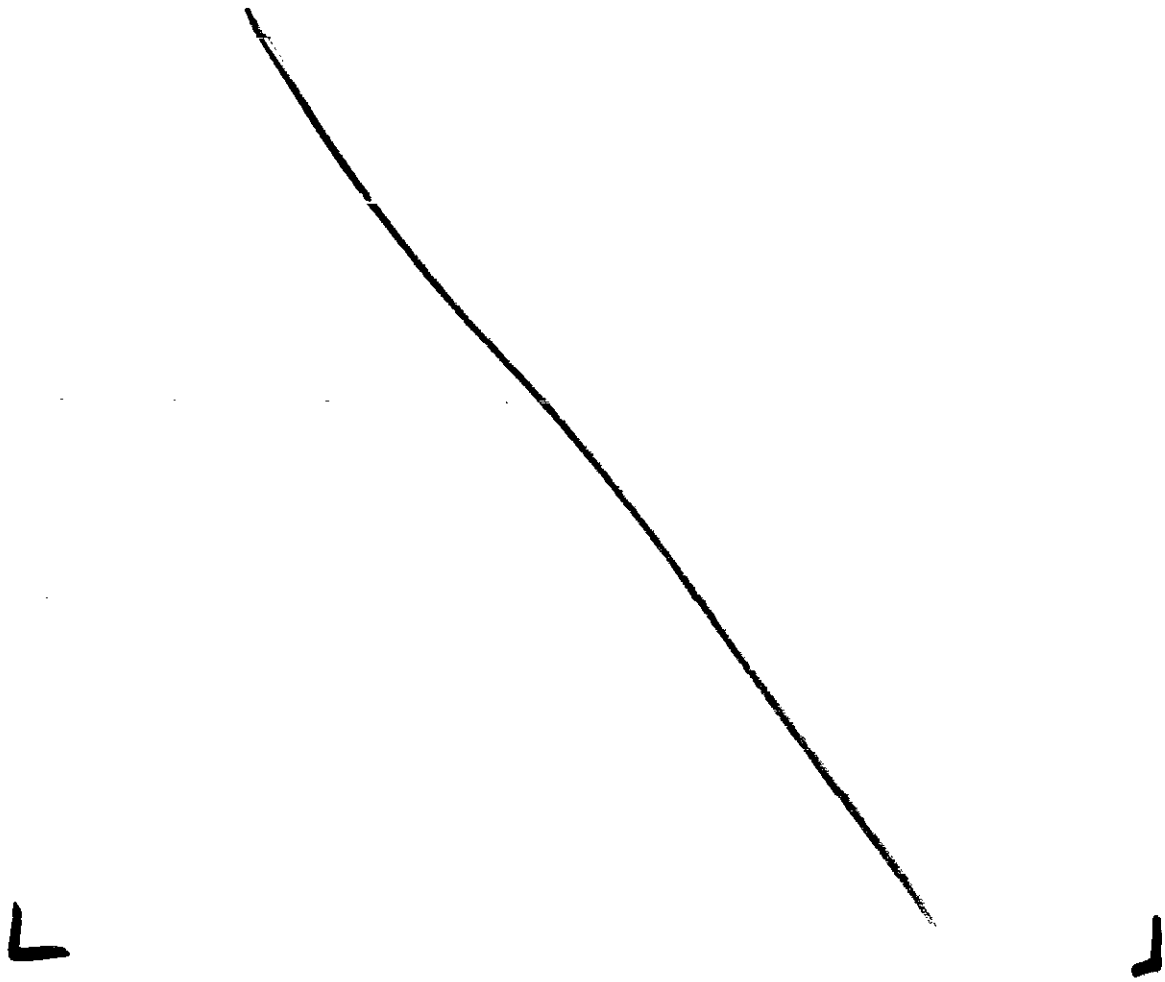
# 4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

__✓__ § 552(b)(5) Draft Labeling

*Withheld Track Number: Microbiology* 1



## 6. RECOMMENDATIONS:

This NDA supplement is approvable pending an accepted version of the label.

Kalavati Suvarna
Microbiologist, HFD-590

**CONCURRENCES:**

HFD-590/Deputy Dir. _____Signature _____Date
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